Supplemental Information Text: Analyzing and Quantifying the Gain-of-Function Enhancement of IP_3 Receptor Gating by Familial Alzheimer's Disease-Causing mutants in Presenilins

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1 Stochastic Scheme of Channel Gating

The gating of IP_3R is given by the 12-state model described in the main text. To determine the state of the channel, we have to determine the transition probabilities at a given time [1, 2]. That is, if the j^{th} channel is in state i, we have to determine the probabilities with which it remains in that state or switches into another state allowed by the kinetic scheme shown in Fig. 1 (main text) within the time interval Δt. For example, if a channel is in state $\mathrm{C}^{\mathrm{L}}_{00}$, possible transitions are to states $\mathrm{C}^{\mathrm{L}}_{20}$ and $\mathrm{C}^{\mathrm{I}}_{04}$. For a sufficiently small time interval Δt, the probabilities for these transitions are given by $P^{(j)}_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{C}^{\mathrm{L}}_{20}} = r_{(\mathrm{C}^{\mathrm{L}}_{00}\to\ \mathrm{C}^{\mathrm{L}}_{20})}\Delta t$ and $P^{(j)}_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{C}^{\mathrm{I}}_{04}} = r_{(\mathrm{C}^{\mathrm{L}}_{00}\to\ \mathrm{C}^{\mathrm{I}}_{04})}\Delta t$. The probability for the channel to remain in state $\mathrm{C}^{\mathrm{L}}_{00}$ is $P_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{C}^{\mathrm{L}}_{00}} = 1 - P_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{C}^{\mathrm{L}}_{20}} - P_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{C}^{\mathrm{I}}_{04}}$. To determine the transition probabilities, we divide the unit interval into three subintervals of length $P_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{i}}\Delta t$, i represent the three states to which the channel can make transition. If a random number drawn from a uniform distribution over the unit interval falls into the subinterval $P_{\mathrm{C}^{\mathrm{L}}_{00}\to\mathrm{i}}\Delta t$, the corresponding transition is performed. The time interval Δt was kept small enough for the linear dependence of $P_{i\to i}$ on the time interval to remain valid. We used a time step of 1 μs for the puff simulations. The channel is open when in any of the states $\mathrm{O}_{14}^{\mathrm{I}}$, $\mathrm{O}_{24}^{\mathrm{I}}$, or $\mathrm{O}_{24}^{\mathrm{H}}$. The above procedure was repeated for all channels.

2 Elements of Tridiagonal Matrix (TM)

Considering a spherical symmetry around the channel, the system of eqs. (26, main text) and (27, main text) converts to a TM system. Here we derive the elements of the TM. The detail derivation of the scheme is given in [3]. This method converts a 3D problem into a 1D problem and is numerically significantly faster than the standard methods such as Crank-Nicolson. In what follows n is the time index and j is the space index in spherical polar coordinates. Using eq. (29, main text), we can write eq. (26, main text) as

$$\frac{c^{(n+1)} - c^{(n)}}{\Delta t} = D\nabla^2 c^{(n+1)} + J\delta(r) + k_d^r(B_d - b_d^{(n)}) - k_d^f c^{(n+1)} b_d^{(n)} \tag{1S}$$

Writing the Laplacian in spherical polar coordinates and considering no-flux boundary conditions we get the elements of lower, middle, and upper diagonal (a_j, b_j, and c_j respectively) of the TM given as

$$a_j = \begin{cases} 0 & \text{if } j = 1 \\ \frac{-D\Delta t}{\Delta r^2}(1 - \frac{1}{2j})^2 & \text{if } j = 2, ...N - 1 \\ \frac{-2D\Delta t}{\Delta t} & \text{if } j = N. \end{cases} \tag{2S}$$

$$b_j = \begin{cases} \frac{6D\Delta t}{\Delta r^2} + 1 + k_d^f b_d^{(n,j)}\Delta t & \text{if } j = 1 \\ \frac{D\Delta t}{\Delta r^2}(1 + \frac{1}{2j})^2 + \frac{D\Delta t}{\Delta r^2}(1 - \frac{1}{2j})^2 + 1 + k_d^f b_d^{(n,j)}\Delta t & \text{if } j = 2, ..N - 1 \\ \frac{2D\Delta t}{\Delta r^2} + 1 + k_d^f b_d^{(n,j)}\Delta t & \text{if } j = N. \end{cases} \tag{3S}$$

$$c_j = \begin{cases} \frac{-6D\Delta t}{\Delta r^2} & \text{if } j = 1 \\ \frac{-D\Delta t}{\Delta r^2}(1 + \frac{1}{2j})^2 & \text{if } j = 2, ...N - 1 \\ 0 & \text{if } j = N. \end{cases} \tag{4S}$$

The right hand side for the TM system for the cytosolic Ca^{2+} concentration is represented by d_j and is

$$d_j = c^{(n,j)} + J\delta(r)\Delta t + k_d^r(B_d - b_d^{(n,j)})\Delta t,\ \text{j=1,..N} \tag{5S}$$

The rate equation for dye buffer can be expanded and solved iteratively in similar fashion.

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Table 1S: Parameters for puff simulations

Quantity	Symbol	—	Numerical Value	Reference
Resting Cytosolic Calcium	Ca_{rest}	=	$50nM$	[4]
Dye Buffer	B_d	=	$20\ \mu M$	
Number of channels	N_{ch}	=	10	[5]
Pore Radius	r_{pore}	=	$2.5nm$	[6, 7]
Channel Spacing	r_{nn}	=	$120nm$	[3, 8]
Ca^{2+}	D_c	=	$0.223\mu m^2/ms$	[9]
Dye	D_d	=	$0.200\mu m^2/ms$	[10]
Dye Buffer	k_d^f	=	$0.15/\mu M ms$	[10, 11]
	k_d^r	=	$0.45/ms$	[10, 11]